Remarks and Arguments

Claims 28, 41, 51 and 70 have been amended. No claims have been cancelled or added. Claims 28-70 remain pending for examination.

Claim rejections 35 USC § 112

Claim 28 now reads ... *having* a *metal surface covered with a polypeptide at 5 to 70% coverage, based on a maximum coverage of the metal surface with a monomolecular layer ...".*

Claim 41 now reads "... *wherein the polypeptide comprises systemic hormones comprisesing* ... ".

Claim 51 now reads "*an osteogenic dental implant having a metal surface and ... the process including the step of applying to a bone surface, in* the *area* of *the cavity, and/or to the metal surface of the implant ... the metal surface is covered with the polypeptide at 5 to 70% coverage, based on a maximum coverage of the metal surface with a monomolecular layer.*"

Claim 70 now reads *"the metal surface is covered with the polypeptide at 8% to 20% coverage".*

Support for these amendments is found, e.g., on page 3 second paragraph, page 5 second paragraph and page 11 second paragraph of the specification.

The term *"at* a *rate* of" does not necessarily relate to a time variable as the Examiner asserts. This term also has the meaning of *"a ratio between two things"* or "*a quantity, amount, or degree of something measured per unit of something else"* (see the enclosed printout of Merriam Webster online dictionary). As the Examiner correctly

states the meaning of the term "*at* a *rate of*" as *"percent surface coated"* is supported by Example 1 and page 11 second paragraph of the specification.

Applicant has amended claims 28 and 51 to recite a % coverage, based on a maximum coverage, consistent with the specification.

The term systemic hormones include several different classes of compounds. These classes are peptides, polypeptides, steroids and derivatives of amino acids, such as thyroxin (see enclosed printouts Benninghoff, Drenckhahn, Anatomie, Band 2, 6. Auflage, Verlag Elsevier, Urban & Fischer Verlag. 2004, page 186, left column, last paragraph (in German) and Sonia Ciarmatori, "The role of IGFIIGFBP system in the proliferation and differentiation of chondrocytes", summary). See also the present specification at page 10 paragraph 6 which lists the specific compounds of claim 41 as systemic hormones and includes literature citations.

In view of the above, the Examiner's rejections regarding clarity are believed to be overcome.

Section 102 Rejection

The Examiner rejects the subject matter of independent claims 28 and 51 as being anticipated by Cole et al as evidenced by Schrier et al and Israel et al.

Cole teaches implants coated with BMP-2 and the ability of BMP-2 to remain osteoinductive and stimulate appositional bone formation. The coating process is described as simple even pipetting of a BMP-2 solution on the implants with subsequent drying in a laminar flow sterile hood. This process usually leads to an irregular protein deposit on the implant surface. Further, the coated implants are implanted in a muscle pouch where they stimulate appositional bone formation. This is an artificial situation which may not be compared to the situation where the implant is positioned in a bone cavity.

Cole does not disclose monomolecular layer (monolayer) and in addition it does also not disclose how this coating is achieved, let alone how a partial monomolecular layer (monolayer) can be obtained. The present invention, however, discloses a partial coating in the form a monolayer of an implant made of titanium metal. Therefore, the subject matter of the independent claims 28 and 51 is not anticipated by Cole. The same applies for the dependent claims.

Section 103 and Double Patenting Rejections

Cole has been discussed above.

Steinemann WO 00/44305 discloses an implant consisting of titanium or a titanium alloy having a roughened, hydroxylated and hydrophilic surface. A method for producing and a method for storing such an implant are also described. There is no coating in general or in the form of a monolayer mentioned.

Since neither Cole nor Steinemann teach a partial coating in the form of a monolayer, the same arguments as set forth in the response to the previous Office Action still apply. The remaining references fail to cure the deficiencies of the primary references.

It is an objective of the present invention to provide an implant with a surface having superior osteointegration properties while avoiding common disadvantages of coatings known in the art.

This objective is achieved with an implant according to claim 28 of the present invention and a process according to claim 51 for introducing said implants.

An implant according to the present invention can be made for instance by sandblasting and subsequent etching of the implant. This treatment yields "active"

binding sites (hydroxyl groups) on the implant surface. By subsequently treating the implant with the desired polypeptide these "active" binding sites allow the forming of a regular and oriented polypeptide monolayer. Without the "active" binding sites the treatment of an implant with a polypeptide would result in a general deposition of protein in an irregular manner and not in the form of a monolayer.

Implants according to the present invention are at least partially coated, that is a coverage of 5 to 70% based on the maximum coverage. The coating comprises polypeptides which form a monolayer on the implant surface. The polypeptides bind directly to the metal surface, there are not intermediates providing for the binding nor are the polypeptides localized in some kind of carrier material as some of the cited references imply.

The coating in the form of a monolayer according to the present invention is not rendered obvious by the documents cited, either alone or in combination. A skilled person who tries to combine the teachings of the documents cited by the Examiner does not achieve a coating as disclosed in the present invention. On the contrary, he achieves an entirely different result.

According to the present invention it is decisive that the coating is not complete but only partial. The preferred range of 8 to 20% indicates that a quite low percentage of coating based on the maximum possible yields the best results. In contrast, all of the cited references if they mention a coating with bone-growth promoting polypeptides at all, tend to favor a maximized coating in terms of the amount of polypeptides and the surface covered. Thus, a skilled person is led in the opposite direction of the teachings of the present invention.

The partial coating is also important with respect to the direct contact of bone cells (e.g. osteoblasts) with the implant surface. The surface provides "space" and attachment sites ("active binding sites") for these cells, which accelerates the formation of a stable implant/bone tissue interface.

The documents cited by the Examiner do not render obvious either alone or in combination the subject matter defined in the claims of the present Invention. Therefore, the subject matter of the independent claims 28, 51 is inventive over the various combinations cited by the Examiner. The same applies for the dependent claims.

The double patenting rejection is believed to be rendered moot in view of the above statements.

Reconsideration and allowance are respectfully requested.

RECONSIDERATION

It is believed that all claims of the present application are now in condition for allowance.

Reconsideration of this application is respectfully requested. If the Examiner believes that a teleconference would expedite prosecution of the present application the Examiner is invited to call the Applicant's undersigned attorney at the Examiner's earliest convenience.

Any amendments or cancellation or submissions with respect to the claims herein is made without prejudice and is not an admission that said canceled or amended or otherwise affected subject matter is not patentable. Applicant reserves the right to pursue canceled or amended subject matter in one or more continuation, divisional or continuation-in-part applications.

To the extent that Applicant has not addressed one or more assertions of the Examiner because the foregoing response is sufficient, this is not an admission by Applicant as to the accuracy of such assertions.

Please grant any extensions of time required to enter this response and charge any fees in addition to fees submitted herewith that may be required to enter/allow this response and any accompanying papers to our deposit account 02-3038 and credit any overpayments thereto.

Respectfully submitted,

/Therese A. Hendricks/ Date:2010-08-02

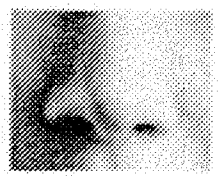
Therese A. Hendricks, Reg. No. 30,389
Rissman Hendricks & Oliverio, LLP
Customer Number 21127
Tel: (617) 367-4600 Fax: (617) 367-4656

rate

Entries 1 to 10 of 20. Next 10

1 rate (verb)
2 rate (noun)
3 rate (verb)

Main Entry: **2rate**
Function: *noun*
Etymology: Middle English, from Anglo-French, from Medieval Latin *rata,* from Latin (*pro*) *rata* (*parte*) according to a fixed proportion
Date: 15th century
1 a : reckoned value **:** VALUATION **b** *obsolete* **:** ESTIMATION



2 *obsolete* **:** a fixed quantity
3 a : a fixed ratio between two things **b :** a charge, payment, or price fixed according to a ratio, scale, or standard: as (1) **:** a charge per unit of a public-service commodity (2) **:** a charge per unit of freight or passenger service (3) **:** a unit charge or ratio used in assessing property taxes (4) *British* **:** a local tax
4 a : a quantity, amount, or degree of something measured per unit of something else <her typing rate was 80 words per minute> **b :** an amount of payment or charge based on another amount; *specifically* **:** the amount of premium per unit of insurance
5 : relative condition or quality **:** CLASS
— **at any rate :** in any case **:** ANYWAY

Learn more about "rate" and related topics at Britannica.com

Pronunciation Symbols

Share this entry:

Link to this page:
rate

Cite this page:

MLA Style
"rate." Merriam-Webster Online Dictionary. 2010.
Merriam-Webster Online. 2 August 2010
<http://www.merriam-webster.com/dictionary/rate>

APA Style
rate. (2010). In *Merriam-Webster Online Dictionary.*
Retrieved August 2, 2010, from http://www.merriam-webster.com/dictionary/rate

Übersicht*

Wirkstoffe. Die Wirkstoffe des endokrinen Systems sind die Hormone (*hormaein*, gr.: antreiben, in Bewegung setzen). Es handelt sich um **primäre** (extrazelluläre) **Botenstoffe**, die an Rezeptoren von Zielzellen binden und deren Funktion beeinflussen. Im Gegensatz zu den Sekreten exokriner Drüsen werden Hormone nicht an Gangsysteme abgegeben, die direkt oder indirekt (über das Verdauungs-, Atem- und Urogenitalsystem) mit der Außenwelt des Organismus in Verbindung stehen. Hormone werden ausschließlich an die **Innenwelt** des Organismus abgegeben. Erfolgt die Abgabe der Hormone in die Blutbahn und erreichen sie dadurch ihre Zielgewebe, spricht man von **endokriner Sekretion** (-Wirkung). Werden die Zielzellen durch Diffusion im weiteren Umfeld erreicht, spricht man von **parakriner Wirkung** (-Sekretion). Viele Hormone wirken zusätzlich auch auf die hormonproduzierenden Zellen selbst (**autokrine Wirkung**). Eine Wirkung auf angrenzende Nachbarzellen wird als **juxtakrine Wirkung** bezeichnet. Juxtakrin wirken auch Neurotransmitter, die allerdings nicht zu den Hormonen gerechnet werden.

Hormone dienen der Kommunikation von Zellen des Organismus untereinander und benutzen die Körperflüssigkeiten als Kommunikationsmedium, **humorale Kommunikation** (*humor*, gr.: Flüssigkeit). Wird der Transport durch die Blutbahn benötigt, um an die Zielzellen zu gelangen, sprechen wir von **systemischen Hormonen**. Wirken die Hormone jedoch hauptsächlich lokal im Umfeld der Hormonabgabe, spricht man von **Gewebehormonen**.

Endokrines System. Zum endokrinen System gehören nur solche Organe (**endokrine Drüsen**, Hormondrüsen) oder Zellen bzw. Zellgruppen (**endokrine Zellen**), deren **Hauptfunktion** und Spezialisierung in Synthese und Abgabe von **systemischen Hormonen** liegt (Tab. 11.1). Ausnahmen bilden sexualhormonproduzierende Zellen der Follikel der Ovarien und der Trophoblast der Plazenta, die auch andere wichtige Funktionen erfüllen. Die systemischen Hormone werden über das Interstitium in die Blutbahn abgegeben und gelangen unter Vermittlung des Herz-Kreislauf-Systems zu ihren Zielgeweben. Deren Funktion wird durch die Hormone spezifisch beeinflusst.

In diesem Kapitel werden nur endokrine Drüsen und endokrine Zellsysteme abgehandelt: **Hypophyse, Schilddrüse, Nebenschilddrüsen, Nebennieren, Endokrines Pankreas, Disseminierte endokrine Zellen** und **Zirbeldrüse**.

Die sexualhormonproduzierenden Zellsysteme in Eierstock, Plazenta und Hoden werden bei den Geschlechtsorganen besprochen (Kap. 8.5, 8.6, 8.7, Bd. 1). Andere hormonproduzierende Zellen und deren systemischen Hormone, wie Herzmuskelzellen der Herzvorhöfe (Hormon: atriales natriuretisches Peptid, ANP) oder Interstitialzellen der Niere (Hormon: Erythropoetin), werden bei den Kapiteln „Herz" und „Niere" besprochen. In der Niere wird auch das Renin-Angiotensin-System abgehandelt, das u.a. die Sekretion von Aldosteron aus der Nebennierenrinde steuert. Eine Übersicht über Gewebehormone (Zytokine, Chemokine, Ausschüttende, Wachstumsfaktoren und More Gastrin) wird in Kap. 2.17.4 u. 3.2.8, Bd. 1 gegeben.

Stoffklassen. Die systemischen Hormone gehören folgenden Stoffklassen an:

1. **Peptide, Polypeptide** (z.B. antidiuretisches Hormon, Insulin, luteinisierendes Hormon)
2. **Steroide** (z.B. Östradiol, Testosteron, Aldosteron)
3. **Aminosäurederivate** (z.B. Adrenalin, Thyroxin, Melatonin).

Peptidhormone (bis 100 Aminosäuren lang) und **Proteinhormone** (über 100 Aminosäuren lang) werden im rauen ER als Vorstufen (**Prohormone**) synthetisiert, im ER und Golgi-Apparat modifiziert (proteolytisch gespalten, glykosiliert) und im Golgi-Apparat in Sekretvesikel (Hormongranula) verpackt. Die Granula werden intrazellulär gespeichert und geben das Hormon durch Exozytose aufgrund spezifischer Stimuli ab.

Steroidhormone sind Lipidverbindungen. Sie leiten sich vom Cholesterol ab und können durch Diffusion die Zellmembran passieren. Sie können deshalb nicht gespeichert werden und werden bei Bedarf neu synthetisiert. Im Blut sind Steroidhormone an Transportproteine gebunden. Erst nach Trennung von den Transportproteinen entsteht das freie Hormon, das teilweise noch lokal in die biologisch aktive Form umgewandelt wird (z.B. Testosteron zu Dihydrotestosteron).

Aminosäurederivate entstehen durch chemische Modifizierungen von Aminosäuren. Sie werden entweder in sekretorischen Granula angereichert (Adrenalin, Melatonin) und auf spezifische Reize hin durch Exozytose freigesetzt oder sie können wie die Schilddrüsenhormone nur als Vorstufen extrazellulär in von Zellen umgebenen Hohlräumen (Follikeln) gespeichert werden und müssen bei Bedarf durch Abspaltung freigesetzt werden.

Wirkmechanismus. Hormone binden an spezifische **Rezeptoren der Zielzellen.** Hydrophile Hormone binden an Rezeptoren auf der Plasmamembran der Zielzellen. Dadurch werden **intrazelluläre Signalwege** (G-Protein-abhängig und -unabhängig) in Gang gesetzt, die verschiedene **Sofortreaktionen** auslösen (z.B. Kontraktion, Sekretion, Glucoseaufnahme) und auch die **Transkription** von spezifischen Genen in den Zielzellen steuern (**verzögerte Reaktion**). Die lipophilen Steroide und Schilddrüsenhormone gelangen durch Diffusion bzw. Transportmechanismen durch die Plasmamembran der Zielzellen in deren Zytosol bzw. Zellkern. Dort binden sie an **zytoplasmatische** und **nukleare Rezeptorproteine.** Zytoplasmatische Rezeptor-Hormon-Komplexe werden anschließend in den Zellkern transloziert. Dort binden die Hormon-Rezeptor-Komplexe an hormonspezifische Promotorelemente von verschiedenen Genen (**hormoneresponsive Gene**).

Regulation. Hormonproduktion und -ausschüttung werden über Regelkreise gesteuert. Dabei kann die **geregelte Größe** die Hormonkonzentration im Blut (z.B. des Schilddrüsenhormons Thyroxin) oder der biologische Effekt des Hormons sein (z.B. Blutglucosekonzentration bei Insulin). Der Sollwert der Regelgröße ist entweder intrinsisch festgelegt (z.B. Blutglucosekonzentration, die in engen Grenzen konstant bleiben muss) oder wird nach aktuellen Erfordernissen des Körpers und der Umweltsituation eingestellt (erhöhter Bedarf an Thyroxin bei gesteigertem zellulärem Energieverbrauch, z.B. im Wachstum oder bei Kälte). Der Istwert der Regelgröße wird über spezifische Messfühler (z.B. durch Hormonrezeptoren oder andere Mechanismen wie Glucoseaufnahme durch Insulin produzierende Zellen) ermittelt.

* Dr. Dr. S. Silbernagl

Sonia Ciarmatori
Dr. sc. hum.

The role of the IGF/IGFBP system in the proliferation and differentiation of chondrocytes

Geboren am 29.07.1970 in Ponte S. Pietro (Italien)
Diplom der Fachrichtung Biologie am 14.05.1996 an der Universität "Universita'statale degli studi di Milano"
Promotionsfach: Kinderheilkunde
Doktorvater: Prof.Dr.med.Burkhard Tönshoff

The major systemic hormones regulating longitudinal bone growth during childhood are growth hormone (GH), insulin-like growth factor (IGF)-I, thyroid hormones and glucocorticoids. Because IGF-I is an important chondrocyte growth factor, we sought to investigate, how it regulates the expression of the IGF binding proteins (IGFBPs), and to examine the intracellular mechanisms, by which exerts two of its pivotal effects, stimulation of proliferation and differentiation.

The bioactivity of IGF-I in the cellular microenvironment is modulated both by inhibitory and stimulatory IGFBPs whose production is under partial control of IGF-I. However, little is known on the IGF-mediated regulation of these IGFBPs in the growth plate. We therefore studied the effect of IGF-I on IGFBP synthesis in rat growth plate chondrocytes in primary culture and the involved distinct intracellular signaling pathways. Under baseline conditions, growth plate chondrocytes expressed mRNA species for IGFBP-2 to -6, determined by RT-PCR. Incubation with IGF-I enhanced IGFBP-3, IGFBP-4 and IGFBP-5 in conditioned cell culture medium in a dose- and time-dependent manner. Coincubation of IGF-I with specific inhibitors of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK)1/2 pathway (PD098059 or U0126) completely abolished IGF-I-stimulated IGFBP-3 gene expression, quantified by RNase protection assay. In contrast, inhibition of the phosphatidylinositol-3 kinase (PI-3 kinase) signaling pathway by LY294002 abrogated both IGF-I-stimulated IGFBP-3 and -5 gene expression. For comparison, IGF-I-driven cell proliferation was mediated both through the MAPK/ERK1/2 and PI-3 kinase pathway. These data suggest that IGF-I modulates its activity in juvenile rat growth plate chondrocytes by the synthesis of both inhibitory (IGFBP-3, IGFBP-4) and stimulatory

(IGFBP-5) binding proteins in a feed-back manner. The finding that IGF-I uses different and only partially overlapping intracellular signaling pathways for the regulation of two IGFBPs with opposing biological functions might be important for the regulation of IGF bioactivity in the cellular microenvironment.

IGF-I promotes both proliferation and differentiation of growth plate chondrocytes *in vitro* and *in vivo*. In order to investigate the pathways involved in the IGF-regulation, we used the mesenchymal chondrogenic cell line RCJ3.1C5.18 (RCJ), which progresses spontaneously to differentiated growth plate chondrocytes. This differentiation process could be enhanced by exogenous IGF-I. Pharmacological inhibition of PI-3 kinase by LY294002, the MAPK/ERK1/2 by U0126 and the protein kinase A (PKA) pathway by H-89 completely surpressed IGF-I-stimulated cell proliferation as assessed by [^{3}H]thymidine incorporation, while blockade of the protein kinase C (PKC) pathway by Bisindolylmaleimide (BIS) had no significant effect. In contrast, IGF-I-induced early cell differentiation, as assessed by collagen type II gene expression, was not affected by MAPK/ERK1/2 pathway inhibition, but almost abolished by inhibition of the PI-3 kinase and PKA pathways. Moreover, middle to late differentiation of chondrocytes in response to IGF-I, as assessed by alcian blue and alkaline phosphatase activity assay, was only interrupted by PI-3 kinase pathway inhibition. The phosphorylation state of Akt downstream of PI-3 kinase was enhanced by inhibition of PKC and/or PKA, whereas PI-3 kinase or PKC inhibition had no effect on the MAPK cascade, as assessed by the ERK1/2 phosphorylation state. The respective protein content of distinct PKC and PKA subunits increased during differentiation. These data suggest that the two crucial cellular responses of chondrocytes to IGF-I, proliferation and differentiation, are mediated by parallel and partially overlapping signaling pathways. Whereas the PI-3 kinase, MAPK/ERK1/2 and PKA pathways subserve the mitogenic action of IGF-I, IGF-I-stimulated cell differentiation is mainly signaled through the PI-3 kinase pathway. Hence, IGF-I exerts its differential effect on chondrocyte proliferation vs. differentiation through the use of at least four partially interacting intracellular signaling pathways, whose activity is temporarily regulated.

Since we have shown previously that intact IGFBP-5 in the presence of IGF-I stimulates chondrocyte proliferation, we decided to examine the role of IGFBP-5 on chondrocyte differentiation, using the RCJ cell line. RCJ cells undergoing spontaneous differentiation markedly upregulated IGFBP-5 synthesis. Transient IGFBP-5 overexpression in RCJ cells in the absence of IGF-I did not promote the expression of the chondrocyte differentiation markers collagen type II and proteoglycan, indicating that IGFBP-5 on its own does not

stimulate chondrocyte differentiation. However, IGFBP-5 overexpression enhanced the process of IGF-I-mediated differentiation of RCJ cells. A potential mechanism for this effect is the specific increase of Akt phosphorylation in IGFBP-5 overexpressing cells in the presence of IGF-I, indicating an increased activity of the PI-3 kinase pathway, while the MAPK/ERK1/2 cascade, was rather downregulated. Furthermore, IGF-I increased IGFBP-5 expression in differentiating chondrocytes by use of three signaling pathways (PI-3 kinase, PKA, and PKC pathway), which are also operative for IGF-I-mediated cell differentiation. The IGF-I-induced IGFBP-5 gene expression required *de novo* mRNA transcription and *de novo* protein synthesis. These data demonstrate that IGFBP-5 enhances growth plate chondrocyte differentiation through an IGF-I-dependent mechanism and imply a role for IGFBP-5 in upregulating IGF action during chondrocyte differentiation *in vivo*.